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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/997,464	12/23/1997	DAVID STERN	54202/JPW/SB	1340

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EXAMINER

ANGELL, JON E

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/997,464

Applicant(s)

STERN ET AL.

Examiner

J. Eric Angell

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,11,12 and 34-37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) _____ is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. This Action is in response to the communication filed on 4/23/03, as Paper No. 28. The amendment has been entered and the specification has been amended as instructed. Claims 1, 3, 4, 11, 12 and 34-37 are currently pending in the application and are examined herein.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/23/03 has been entered.

It is noted that the amendment filed 4/23/03 did not amend any of the pending claims. Furthermore, the response filed 4/23/03 did not contain any arguments pertaining to the rejections of record. Therefore, all pending claims remain rejected for the reasons of record, which are summarized below.

Claim Rejections - 35 USC § 112, first paragraph

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 11 and 12 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record. A summary of the rejection follows.

Claim 11 is drawn to a pharmaceutical composition which comprises a compound which inhibits neurotoxicity in a cell by inhibiting interaction between receptor for advanced glycation end product (RAGE) and mutant presenilin-2 identified by the method of claim 1, and a pharmaceutically acceptable carrier. The claim encompasses a genus composed of all compounds that inhibit the interaction of RAGE and mutant presenilin-2. However, the specification does not disclose a single species compound that inhibits the interaction of RAGE and mutant presenilin-2. Therefore, the disclosure is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of a compound that inhibits the interaction of RAGE and mutant presenilin-2 at the time the application was filed. Thus, the written description requirement is not satisfied for the claimed genus. Claim 12 is a dependent claim and is therefore rejected for the same reason.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Art Unit: 1635

4. Claims 1, 3, 4, 11, 12 and 34-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wolozin *et al.* (Science, 274:1710-1713; December 6, 1996) taken with Yan *et al.* (Nature 328:685-691, 1996) for the reasons of record. A summary of the rejection follows.

The claimed invention is drawn to a method of evaluating the ability of a compound to inhibit neurotoxicity and pharmaceutical compositions comprising the compounds identified by the method.

Wolozin teaches expressing presenilin-2 or mutant presenilin-2 (e.g. N141I) in PC12 cells and treating the cells with amyloid- β results in increased apoptosis compared to untransfected controls (see figure 4). In addition, Wolozin *et al.* disclose a method comprising a) culturing the neuronally differentiated PC12 cells in the presence or absence of a compound, i.e. pertussis toxin or amyloid- β (1-42), b) determining the level of apoptosis in the control and treated cells, and c) comparing the extent of the apoptotic activity in the cells cultured in the presence of the compound compared to cells cultured in the absence of the compound to evaluate the effect of the compound on apoptotic activity (see, e.g., page 1713, note #21).

Wolozin does not teach that the PC12 cells are transfected with a DNA sequence encoding RAGE and which is transfected in PC12 cells.

Yan teaches that enhanced expression of RAGE in Alzheimer's disease, in affected neurons, in microglial and in vasculature, is consistent with the concept that amyloid- β -RAGE interaction may contribute to neurotoxicity that results in dementia (see page 382, left column, last paragraph). Yan indicates that RAGE can mediate amyloid- β induced oxidant stress on endothelium and neuronal cells and that the stress can be prevented by blocking access to RAGE using either anti-RAGE IgG or excess soluble receptor, and further teach that expression of

RAGE increases vulnerability to amyloid- β . Yan also teaches that RAGE, if present and/or upregulated in cells important in the pathogenesis of Alzheimer's' disease, could mediate toxic effects when associated with amyloid- β . Finally, Yan teaches transfection of RAGE into COS-1 cells and the use of these transfected cells in analyzing the effect of compounds on amyloid- β activity with respect to oxidant stress (see, e.g., p 688 under "RAGE and amyloid- β -induced cellular stress).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention was made to modify the method of Wolozin *et al.* by further modifying the presenilin-2 transfected PC12 cells of Wolozin *et al.* by transfecting the cells with a vector encoding RAGE in view of the teachings of Yan *et al.* that cells transfected with RAGE are useful in studying the interaction of RAGE and amyloid- β on oxidant stress and cytotoxicity in cells.

It is pointed out that one of ordinary skill in the art would have been motivated to provide such a modified PC12 cell to use in a method of identifying inhibitors of neurotoxic compounds, in view of the teachings of Yan *et al.* that expression of RAGE in Alzheimer's disease, in affected neurons, in microglial, and in vasculature, is consistent with the concept that amyloid- β -interaction may contribute to neurotoxicity that results in dementia. Although there was no indication in either Wolozin or Yan that an interaction between amyloid- β and presenilin-2 existed, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Wolozin *et al.* with the teachings of Yan in order to create cells that have a greater sensitivity to amyloid- β neurotoxicity than cells

Art Unit: 1635

expressing either mutant PS2 or RAGE, for the purpose of identifying compounds that inhibit neurotoxicity.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.


Art Unit: 1635

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
May 14, 2003


DAVID T. NGUYEN
PRIMARY EXAMINER